CLAIMS

1. A process for the manufacturing of NO-donating compounds comprising;step **1**,

$ML_{T1}A_{T2}$-COOH + HO-X-OH→ $ML_{T1}A_{T2}$-COO-X-OH

(I) (II)

using an acidic or dehydrating agent and a solvent, optionally followed by purification using extraction or crystallisation, and

step **2**, $ML_{T1}A_{T2}$-COO-X-OH + RSO_2Cl → $ML_{T1}A_{T2}$-COO-X-OSO_2R,

(II) (III)

using a solvent, a base and optionally a catalyst, followed by purification using extraction and crystallisation, and

step **3**,

$ML_{T1}A_{T2}$-COO-X-OSO_2R + Y-NO_m → $ML_{T1}A_{T2}$-COO-X-ONO_m

(III) (IV)

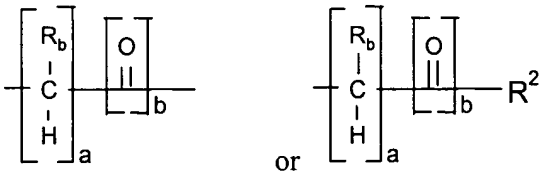
using a solvent and optionally a catalyst,

optionally followed by a crystallisation process for obtaining the compound of formula IV in a substantially crystalline form, and

wherein:

M is a radical of a physiologically active compound;

L is O, S, (CO)O, (CO)NH, (CO)NR^1, NH, NR^1, wherein R^1 is a linear or branched alkyl group, or



wherein R_b is H, $C_{1\text{-}12}$alkyl or $C_{2\text{-}12}$alkenyl;

R^2 is (CO)NH, (CO)NR^1, (CO)O, or CR^1 and a and b are independently 0 or 1;

A is a substituted or unsubstituted straight or branched alkyl chain;

X is a carbon linker;

R is selected from the group consisting of C_1-C_8 alkyl, phenyl, phenylmethyl, C_1-C_4 alkylphenyl, halophenyl, nitrophenyl, acetylaminophenyl, halogen, CF_3 and *n*-C_4F_9;

Y-NO_3 is lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zinc nitrate or tetraalkylammonium nitrate (wherein alkyl is a C_1-C_{18}-alkyl, which may be straight or branched);

m is 1 or 2; and

T1 and T2 are each independently 0, 1, 2 or 3;

with the proviso that

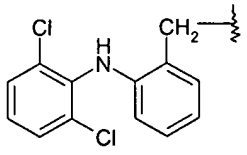
when $ML_{T1}A_{T2}$-COOH is naproxen then X is not $(CH_2)_4$.

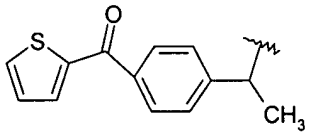
2. The process according to claim 1 wherein group M is part of a molecule of an NSAID, COX 1 or COX 2 inhibitor.

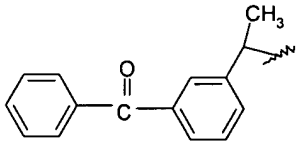
3. The process according to claim 1 wherein X is selected from the group consisting of linear $-(CH_2)_{w1}-$ wherein w1 is an integer of from 2 to 6; $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-C_6H_4-CH_2-$.

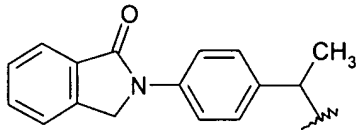
4. The process according to claim 1 wherein R is selected from the group consisting of C_1-C_8 alkyl, phenyl, phenylmethyl, C_1-C_4 alkylphenyl, halophenyl, nitrophenyl, acetylaminophenyl and halogen.

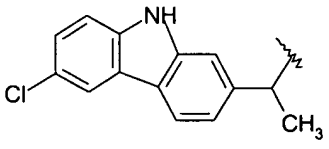
5. The process according to claim 1 wherein the group $ML_{T1}A_{T2}$ is selected from the group consisting of

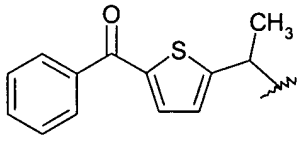


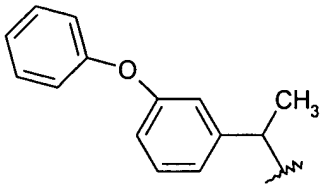
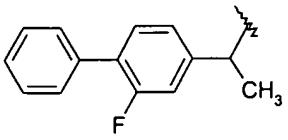
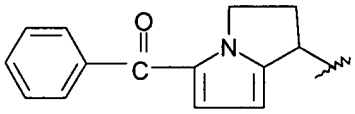
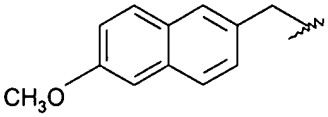
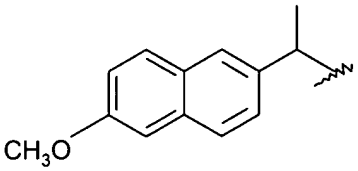
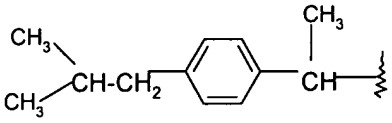




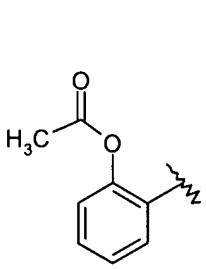
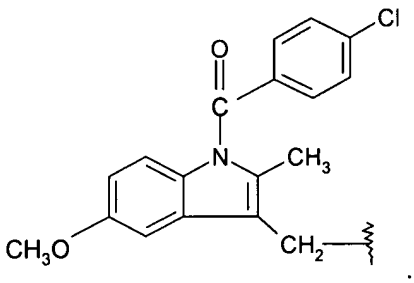




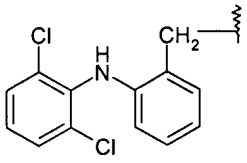


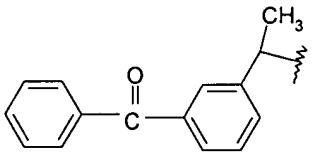
and

6. The process according to claim 5 wherein the group $ML_{T1}A_{T2}$ is



or



7. The process according to any one of claims 1 to 6, whereby the crystallisation process for compound of formula IV comprises the following steps:

a) i) dissolving the compound in a solvent;

or,

ii) extracting the compound from the reaction solution into a solvent;

or,

iii) starting from the reaction solution comprising said compound;

b) vaporating the solvent;

c) adding an anti-solvent and/or cooling

d) isolating the crystals formed, and optionally;

e) recrystallising the crystals formed in step c); or isolated in step d).

8. The process according to claim 7, whereby the crystallisation process for compound 2-[2-(nitrooxy)-ethoxy]ethyl{2-[(2,6-dichlorophenyl)amino]phenyl}acetate (IVa) comprises the following steps:

a) extracting the compound from the reaction solution into a solvent;

b) evaporating the solvent;

c) adding an anti-solvent and/or cooling

d) isolating the crystals formed, and optionally;

e) recrystallising the crystals formed in step c); or isolated in step d).

9. The process according to any one of claims 1 to 8 whereby an acidic or dehydrating agent in step **1** is selected from the group consisting of sulphuric acid or its salts, perchloric acid (e.g. 70%) or other suitable acids such as polystyrene sulphonic acids, zeolites, acidic clays, sand in combination with strong hydrophilic acids such as perchloric acid or gaseous hydrogen chloride and montmorillonites.

10. The process according to any one of claims 1 to 8 whereby the solvent in step **1** is a non-polar and/or non acidic solvent.

11. The process according to any one of claims 1 to 10 whereby the solvents in step **2** are selected from a group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate and isopropyl acetate.

12. The process according to any one of claims 1 to 10 whereby the base in step **2** is triethylamine or *N*-methylmorpholine.

13. The process according to any one of claims 1 to 10 whereby the catalyst in step **2** is 4-(dimethylamino)pyridine.

14. The process according to any one of claims 1 to 13 whereby the compound of formula III in step **2** is crystallised from an organic solvent.

15. The process according to claim 14 whereby an antisolvent is used in the crystallization of compound of formula III in step **2.**

16. The process according to any one of claims 1 to 15 whereby the nitrate sources Y-NO_3 in step **3** is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate and calcium nitrate, or mixtures thereof.

17. The process according to any one of claims 1 to 15 whereby the organic solvent in step **3** is selected from the group consisting of *N*-methylpyrrolidinone, sulpholane, tetramethylurea, 1,3-dimethyl-2-imidazolidinone, acetonitrile, methyl isobutylketone, ethyl acetate, butyl acetate and isopropyl acetate, or mixtures thereof.

18. The process according to any one of claims 1 to 15 whereby the phase transfer-catalyst in step **3** is selected from the group consisting of tetraalkylammonium salt, arylalkylammonium salt, tetraalkylphosphonium salt, arylalkylphosphonium salt, crown ether, pentaethylene glycol, hexaethylene glycol and polyethylene glycols, or mixtures thereof.

19. The process according to any one of claims 7 or 8 whereby the solvent in step a) is selected from the group comprising of lower alkyl acetates, lower alkyl alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, heteroaromatic hydrocarbons, dialkyl ketones, dialkyl ethers, nitriles and water, or mixtures thereof.

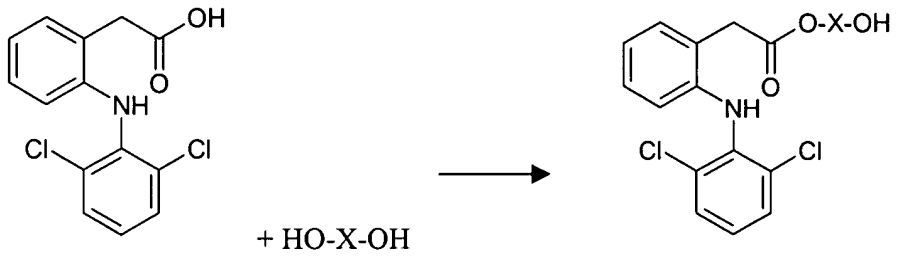
20. The process according to any one of claims 7 or 8 whereby the the antisolvent in step b) of the crystallisation process is selected from the group comprising of ethanol or 2-propanol, toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes and cycloheptanes, or mixtures thereof.

21. The process according to any one of claims 7 or 8 whereby the solvent in step d) is selected from the group consisting of toluene, cumene, xylenes, methyl *iso*-butyl ketone, di-*n*-butyl ether, *tert*-butyl methyl ether, tetrahydrofuran, acetonitrile, *n*-butyl acetate and dichloromethane, or mixtures thereof.

22. The process according to any one of claims 1 to 21 whereby the temperature is between -40°C and 120°C.

23. A process for the manufacturing of NO donating diclofenac of formula IVa, IVb or IVc, comprising:

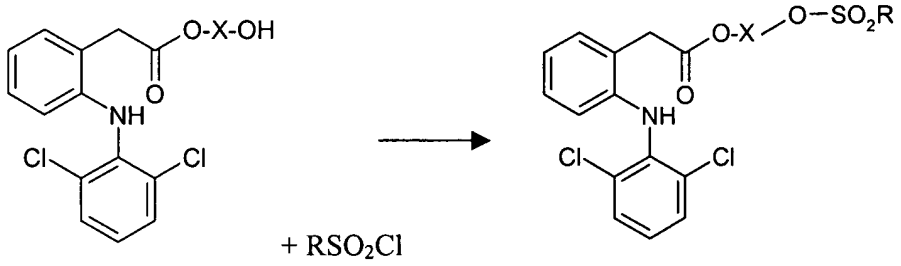
step **1**, reacting a compound of formula Ia with HO-X-OH, wherein X is $C_2H_4OC_2H_4$, C_4H_8 or $C_2H_4OC_2H_4OC_2H_4$, to obtain compounds of formula IIa, IIb or IIc,



diclofenac (Ia) II,

followed by,

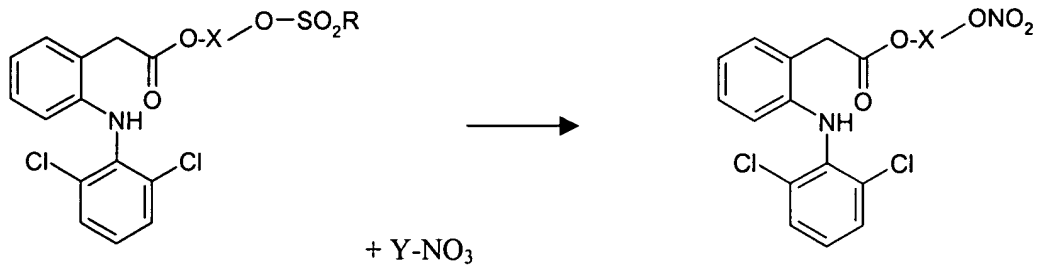
step **2**, reacting the compounds of formula IIa, IIb or IIc with RSO_2Cl, wherein R is as defined above, to obtain compounds of formula IIIa, IIIb or IIIc,



II III,

followed by,

step **3**, reacting the compounds of formula IIIa, IIIb or IIIc with a nitrate source $Y\text{-}NO_3$, wherein Y is as defined above, to obtain compounds of formula IVa, IVb or IVc,



III IV,

followed by,

crystallising the compounds of formula IVa, IVb or IVc using the following steps:

a) extracting the compound from the reaction solution into a solvent;

b) evaporating the solvent;

c) adding an anti-solvent and/or cooling

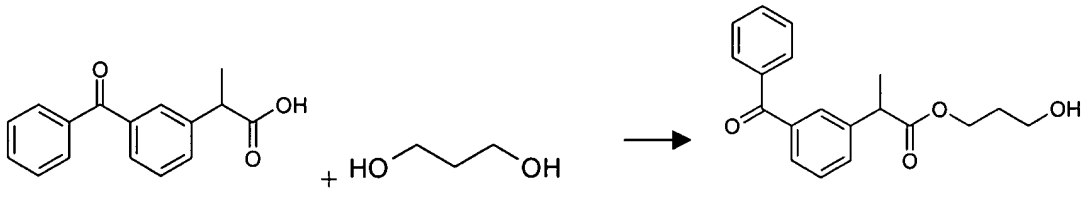
d) isolating the crystals formed, and optionally;

e) recrystallising the crystals formed in step c); or isolated in step d).

24. The process according to any one of claims 1 to 23 whereby the chemical purity of Form A of compound IVa is above 95%.

25. A process for the manufacturing of NO donating ketoprofen of formula IVd comprising:

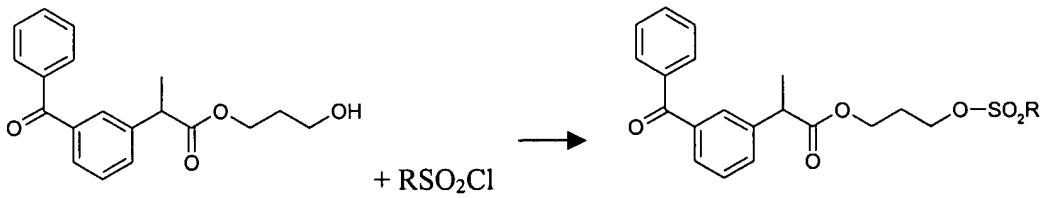
step **1**, reacting a compound of formula Id with 1,3-propanediol to obtain a compound of formula IId,



Id IId

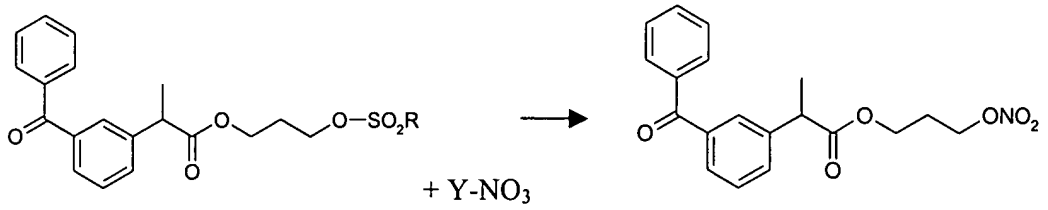
followed by,

step **2**, reacting the compound of formula IId with RSO_2Cl, wherein R is as defined in claim 1, to obtain a compound of formula IIId,



IId IIId

step **3**, reacting the compound of formula IIId with a nitrate source $Y\text{-}NO_3$, wherein Y is as defined in claim 1, to obtain a compound of formula IVd,



IIId IVd.

26. The process according to claim 25 for the manufacturing of the *S*-enantiomer of NO donating ketoprofen of formula IVd.

27. 2-[2-(nitrooxy)ethoxy]-ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (IVa) in a substantially crystalline form.

28. The compound according to claim 27 in anhydrate form.

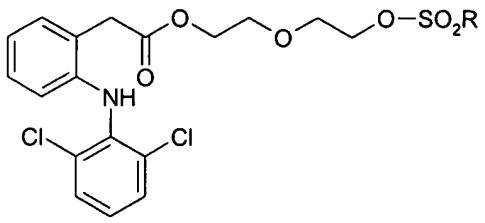
29. The compound according to claim 27 characterised by the major peaks in the X-ray powder diffractogram shown in the table below

D /Å	Relative		D/Å	Relative
12.7	M		3.52	M
8.7	W		3.49	M
8.1	W		3.44	W
6.3	S		3.41	VS
5.94	M		3.31	W
5.91	M		3.28	M
5.58	M		3.17	S
5.34	M		3.15	S
5.05	W		3.13	W
4.50	S		3.06	M
4.48	S		3.04	W
4.38	M		2.97	M
4.35	M		2.96	M
4.28	M		2.81	W
4.23	S		2.70	M
4.08	S		2.68	M
4.06	S		2.64	M
3.96	S		2.60	W
3.78	S		2.54	W
3.76	S		2.43	W
3.55	W			

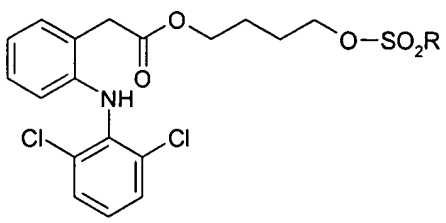
30. The compound according to claim 27 characterised by having a monoclinic unit cell with parameters a = 13.79 Å, b = 11.90 Å, c = 13.01 Å, $\alpha = 90°$, $\beta = 94.0°$, $\gamma = 90°$.

31. A process for the production of Form A of compound IVa which comprises crystallising 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate.

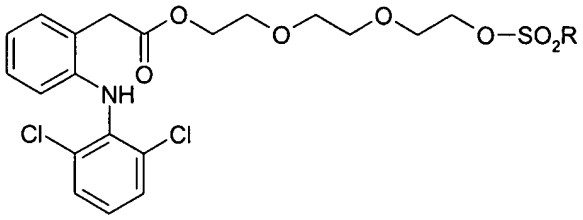
32. Compounds of formula IIIa, IIIb, IIIc and IIId:



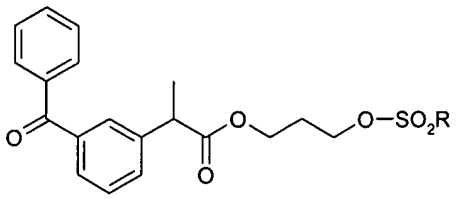
IIIa



IIIb



IIIc



IIId

wherein R is selected from the group consisting of C_1-C_8 alkyl, phenyl, phenylmethyl, C_1-C_4 alkylphenyl, halophenyl, nitrophenyl, acetylaminophenyl, halogen, CF_3 and *n*-C_4F_9.

33. Use of the process according to any one of claims 1 to 21 for the large scale manufacturing of the compounds of formula IVa, IVb, IVc and IVd.

34. Use of the compounds of formula III, $ML_{T1}A_{T2}$-X-O-SO_2R, wherein M, L, A, T1, T2, X and R are as defined in claim 1, as an intermediate for the manufacturing of a pharmaceutically active compound.

35. Use of intermediate compounds of formula IIIa, IIIb, IIIc and IIId as defined in claim 32, prepared according to the process described under step **1** and **2** of claim 1, for the manufacturing of a medicament for the treatment of pain and/or inflammation.

36. Use of Form A of compound IVa for the manufacturing of a medicament.

37. Use of Form A of compound IVa for the manufacturing of a medicament for the treatment of pain and/or inflammation.

38. A pharmaceutical formulation comprising a therapeutically effective amount of Form A of compound IVa, optionally in association with diluents, excipients or carriers.